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=> file drugu drugnl uspatfull biotechno

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FILE 'DRUGU' ENTERED AT 13:44:45 ON 06 DEC 2000
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=> s peptid? librar? (s) (screening or assay?)

L1 784 PEPTID? LIBRAR? (S) (SCREENING OR ASSAY?)

=> s l1 (p) (molecular weight or charge or hydrophob? or isoelect? or whole molecule)

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L4 (P) '
L2 28 L1 (P) (MOLECULAR WEIGHT OR CHARGE OR HYDROPHOB? OR ISOELECT?
OR WHOLE MOLECULE)

=> d tot ti ibib abs

L2 ANSWER 1 OF 28 DRUGU COPYRIGHT 2000 DERWENT INFORMATION LTD
TI Discovery of a novel, potent and specific family of factor Xa inhibitors
via combinatorial chemistry.
ACCESSION NUMBER: 1998-09821 DRUGU C P B
TITLE: Discovery of a novel, potent and specific family of factor Xa
inhibitors via combinatorial chemistry.
AUTHOR: Ostrem J A; Al Obeidi F; Safar P; Safarova A; Stringer S K;
Patek M; Cross M T; Spoonamore J; LoCascio J C
CORPORATE SOURCE: Hoechst-Roussel
LOCATION: Tucson, Ariz., USA
SOURCE: Biochemistry (37, No. 4, 1053-59, 1998) 5 Fig. 3 Tab. 33 Ref.
CODEN: BICHAW ISSN: 0006-2960
AVAIL. OF DOC.: Selectide Corporation, 1580 East Hanley Boulevard, Tucson,
Arizona 85737, U.S.A. (e-mail: jim.ostrem@hmrag.com).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-09821 DRUGU C P B
AB A series of low ***molecular*** ***weight*** peptide inhibitors
of factor Xa was identified by ***screening*** a combinatorial
peptide ***library*** composed of L-amino acids. The
peptides were subsequently modified into SEL-1915, SEL-2219, SEL-2489 and

SEL-2711. The modified compounds were evaluated for inhibitory activity against factor Xa, thrombin, factor VIIa/tissue factor, plasmin, activated protein C, kallikrein and trypsin in-vitro. Furthermore, the in-vitro and in-vivo anticoagulant activities of the compounds were investigated in rabbit pooled plasma and after i.v. administration to rats and rabbits, respectively. The results showed that SEL-2489 was active in in-vitro and in-vivo coagulation ***assays*** , indicating its potential application in anticoagulant therapy.

ABEX The low ***molecular*** ***weight*** peptides initially identified were evaluated for inhibitory activity against factor XA, thrombin and trypsin. All of the peptides containing the Tyr-Ile-Arg or Phe-Ile-Arg tripeptide sequence displayed activity against factor Xa with Ki values in the range 4-15 uM. Little effect on factor Xa inhibition was seen with the removal of 3 to 4 residues from the C-terminus. However, further truncations significantly reduced the Ki values (Ki = 1.4 for D-Tyr-Ile-Arg). Factor Xa activity was completely abolished by the removal of tyrosine from the N-terminus, the replacement of isoleucine with glycine or alanine and the replacement of arginine with lysine or other amino-alkyl side chains. Ac-Tyr-Ile-Arg exhibited potent inhibitory activity against trypsin and thrombin (Ki = 0.5 and 8.2 nM, respectively), but inhibited factor Xa with a low micromolar affinity (Ki = 3.4 uM). The SAR of the initial low ***molecular*** ***weight*** peptides led to the synthesis of SEL-1915, SEL-2219, SEL-2489 and SEL-2711. All of the compounds showed factor Xa inhibitory activity with respective Ki values of 4, 0.055, 0.025 and 0.003 uM for SEL-1915, SEL-2219, SEL-2489 and SEL-2711. The most selective activity for factor Xa over thrombin, factor VIIa/tissue factor, plasmin, activated protein C, kallikrein and trypsin was displayed by SEL-2489. Furthermore, SEL-2489 inhibited prothromboplastin-induced coagulation in-vitro with an IC50 value of 0.9 uM. In the in-vivo studies, SEL-2489 dose-dependently inhibited anticoagulation in rats and rabbits. (ALT)

L2 ANSWER 2 OF 28 DRUGU COPYRIGHT 2000 DERWENT INFORMATION LTD

TI 'Targeted' molecular diversity: design and development of non-peptide antagonists for cholecystokinin and tachykinin receptors.

ACCESSION NUMBER: 1997-10237 DRUGU C P

TITLE: 'Targeted' molecular diversity: design and development of non-peptide antagonists for cholecystokinin and tachykinin receptors.

AUTHOR: Horwell D; Pritchard M; Raphy J; Ratcliffe G

CORPORATE SOURCE: Parke-Davis

LOCATION: Cambridge, U.K.

SOURCE: Immunopharmacology (33, No. 1-3, 68-72, 1996) 2 Fig. 2 Tab. 14 Ref.

CODEN: IMMUDP ISSN: 0162-3109

AVAIL. OF DOC.: Parke-Davis Neuroscience Research Centre, The Forvie Site, Robinsin Way, Cambridge, CB2 2QB, England.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AN 1997-10237 DRUGU C P

AB A drug design strategy was described for non-peptide small molecule antagonists of neuropeptides, starting from substance P and CCK-36-33. The strategy targeted the molecular diversity which exists in the privileged data set of the physico-chemical properties represented by the

side-chains of the 20 genetically encoded amino-acids. The strategy was exemplified by the design of a selective and high affinity CCK-A antagonist PD-140548, CCK-B antagonist PD-134308, tachykinin NK-1 antagonist PD-154075 and NK-2 antagonist Cam-2291. The NK-3 antagonists PD-157672 and the non-peptide PD-161182, were developed from an information-rich dipeptide library constructed from 256 N-protected dipeptides and 64 ***hydrophobic*** biased dipeptides. Pharmacological data was reported for PD-154075 and PD-161182 in guinea-pig, rabbit and human tissues and in-vivo in guinea-pigs. (conference paper).

ABEX A drug design strategy was described for the production of non-peptide small molecule antagonists of neuropeptides, starting from the chemical structure of substance P and CCK-36-33 (sulfated). The strategy targeted the molecular diversity which exists in the privileged data set of the physico-chemical properties represented by the side-chains of the 20 genetically encoded amino-acids. The strategy was exemplified by the design of a selective and high affinity CCK-A antagonist PD-140548, CCK-B antagonist CI-988 (PD-134308), tachykinin NK-1 antagonist PD 154075 and NK-2 antagonist Cam-2291. The NK-3 antagonists PD-157672 and the non-peptide PD-161182, were developed from an information-rich dipeptide library constructed from 256 N-protected dipeptides and 64 ***hydrophobic*** biased dipeptides. The results of binding ***assays*** revealed the Ki of PD-154075 to be 0.35 nM vs. NK1 (IM-9). Ki values were greater than 1 uM for NK2 and NK3 receptors. KB values were 0.33, 1.8, 0.44 and 0.16 in guinea-pig ileum, guinea-pig trachea, rabbit jugular vein and guinea-pig basilar artery, respectively. ID50 of i.v. PD-154075 in a guinea-pig bladder extravasation study was 0.02 mg/kg. In binding ***assays*** using NK3 (human/CHO cells), NK3 (guinea-pig cortical membranes), NK3 (rat cerebral cortex), NK1 (IM9) and NK2 (HUB), IC50 of PD-161182 were 7, 4, 32, 3000 and 786 nM respectively. In-vitro, Ke was 0.9 and 6 Nm in human/CHO cells and guinea-pig habenulae, respectively. PD-161182 is the first example of a high affinity non-peptide antagonist for a membrane-bound receptor developed from ***screening*** a synthetic ***peptide*** ***library*** . (KP)

L2 ANSWER 3 OF 28 DRUGNL COPYRIGHT 2000 IMSWORLD

TI RAPiD Peptide Therapeutics licensing offer, Worldwide
ACCESSION NUMBER: 97:2735 DRUGNL
TITLE: RAPiD Peptide Therapeutics licensing offer, Worldwide
SOURCE: R&D Focus Drug News (25 Aug 1997).
WORD COUNT: 167

L2 ANSWER 5 OF 28 USPATFULL
TI High throughput screening assay systems in microscale fluidic devices
ACCESSION NUMBER: 2000:157233 USPATFULL
TITLE: High throughput screening assay systems in microscale fluidic devices
INVENTOR(S): Parce, John Wallace, Palo Alto, CA, United States
Kopf-Sill, Anne R., Portola Valley, CA, United States
Bousse, Luc J., Menlo Park, CA, United States
PATENT ASSIGNEE(S): Caliper Technologies Corp., Mountain View, CA, United States (U.S. corporation)

NUMBER DATE

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PATENT INFORMATION: US 6150180 20001121
APPLICATION INFO.: US 1999-360782 19990726 (9)
RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-671987, filed on 28 Jun 1996, now patented, Pat. No. US 5942443

NUMBER DATE
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PRIORITY INFORMATION: US 1996-15498 19960416 (60)
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Chin, Christopher L.
ASSISTANT EXAMINER: Pham, Minh-Quan K.
LEGAL REPRESENTATIVE: Murphy, Matthew B.; Shaver, Gulshan H.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 1480
AB The present invention provides novel microfluidic devices and methods that are useful for performing high-throughput screening assays. In particular, the devices and methods of the invention are useful in screening large numbers of different compounds for their effects on a variety of chemical, and preferably, biochemical systems.

L2 ANSWER 6 OF 28 USPATFULL
TI High throughput screening assay systems in microscale fluidic devices
ACCESSION NUMBER: 2000:40901 USPATFULL
TITLE: High throughput screening assay systems in microscale fluidic devices
INVENTOR(S): Parce, J. Wallace, Palo Alto, CA, United States
Kopf-Sill, Anne R., Portola Valley, CA, United States
Bousse, Luc J., Menlo Park, CA, United States
PATENT ASSIGNEE(S): Caliper Technologies Corporation, Palo Alto, CA, United States (U.S. corporation)

NUMBER DATE
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PATENT INFORMATION: US 6046056 20000404
APPLICATION INFO.: US 1996-761575 19961206 (8)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-671987, filed on 28 Jun 1996

NUMBER DATE
---------- --------
PRIORITY INFORMATION: US 1996-15498 19960416 (60)
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Chin, Christopher L.
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew, LLP; Murphy, Matthew B.; Quine, Jonathan Alan
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 20 Drawing Figure(s); 17 Drawing Page(s)
LINE COUNT: 1669
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides novel microfluidic devices and methods that are useful for performing high-throughput screening assays. In

particular, the devices and methods of the invention are useful in screening large numbers of different compounds for their effects on a variety of chemical, and preferably, biochemical systems.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 7 OF 28 USPATFULL
TI Substrate specificity of a protein kinases
ACCESSION NUMBER: 1999:166798 USPATFULL
TITLE: Substrate specificity of a protein kinases
INVENTOR(S): Cantley, Lewis C., Cambridge, MA, United States
Songyang, Zhou, Brookline, MA, United States
PATENT ASSIGNEE(S): Beth Israel Hospital, Boston, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6004757	19991221
APPLICATION INFO.:	US 1995-369643	19950106 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-178570, filed on 7 Jan 1994, now patented, Pat. No. US 5532167, issued on 2 Jul 1996
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Celsa, Bennett
LEGAL REPRESENTATIVE: Testa, Hurwitz & Thibeault, LLP
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 16 Drawing Page(s)
LINE COUNT: 3370
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a method for determining an amino acid sequence motif for a phosphorylation site of a protein kinase. In the method of the invention, a protein kinase is contacted with an oriented degenerate peptide library, peptides within the library which are substrates for the kinase are converted to phosphopeptides and the phosphopeptides are separated from non-phosphorylated peptides. The isolated phosphopeptides are sequenced and an amino acid sequence motif for the phosphorylation site is determined based upon the relative abundance of different amino acids residues at each degenerate position. The invention also provides peptide substrates for protein kinase A, cell cycle control kinases (including cyclin B/p33.sup.cdc2 and cyclin A/p33.sup.CDK2), src family kinases (including pp60.sup.c-src and pp60.sup.v-src), EGF receptor, p92.sup.c-fps/fes, lck, c-abl, PDGF receptor, FGF receptor, insulin receptor, casein kinase II, NIMA kinase, phosphorylase kinase, Cam kinase II and Erk1 based upon amino acid sequence motifs for the phosphorylation sites of these kinases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 8 OF 28 USPATFULL
TI High throughput screening assay systems in microscale fluidic devices
ACCESSION NUMBER: 1999:99591 USPATFULL
TITLE: High throughput screening assay systems in microscale fluidic devices
INVENTOR(S): Parce, John Wallace, Palo Alto, CA, United States
Kopf-Sill, Anne R., Portola Valley, CA, United States

Bousse, Luc J., Menlo Park, CA, United States
PATENT ASSIGNEE(S): Caliper Technologies Corporation, Palo Alto, CA. United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5942443	19990824
APPLICATION INFO.:	US 1996-671987	19960628 (8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-15498	19960416 (60)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Housel, James C.
ASSISTANT EXAMINER: Portner, Ginny Allen
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew; Murphy, Matthew B.; Quine, Jonathan Alan
NUMBER OF CLAIMS: 71
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 1730
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Microfluidic devices and methods that are useful for performing high-throughput screening assays. In particular, the devices and methods of the invention are useful in screening large numbers of different compounds for their effects on a variety of chemical, and preferably, biochemical systems.

L2 ANSWER 12 OF 28 USPATFULL
TI Expression cloning of c-src SH3-domain binding proteins
ACCESSION NUMBER: 96:67930 USPATFULL
TITLE: Expression cloning of c-src SH3-domain binding proteins
INVENTOR(S): Searfoss, III, George H., Birdsboro, PA, United States
Ivashchenko, Yuri D., Audubon, PA, United States
Jaye, Michael C., Glenside, PA, United States
South, Victoria J., Audubon, PA, United States
French, Stephen M., Phoenixville, PA, United States
Cheadle, Christopher, West Chester, PA, United States
Ricca, George A., Blue Bell, PA, United States
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5541109	19960730
APPLICATION INFO.:	US 1994-230047	19940419 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Lau, Kawai
LEGAL REPRESENTATIVE: Smith, Julie K.; Goodman, Rosanne; Parker, III, Raymond S.
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 1614
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a unique SH3 binding domain core motif of the sequence RPLPXXP and cDNA clones encoding proteins which interact with the SH3 domain of c-src, as well as the amino acid sequences which mediate this binding.

Another embodiment of this invention is a method of identifying SH3-binding proteins and elucidating the sequences which mediate binding. This method may be used as an assay to select compounds which bind to this site and which inhibit or enhance the binding of the SH3 domain.

L2 ANSWER 17 OF 28 BIOTECHNO COPYRIGHT 2000 Elsevier Science B.V.
TI The difference in recognition of terminal tripeptides as peroxisomal targeting signal I between yeast and human is due to different affinities of their receptor Pex5p to the cognate signal and to residues adjacent to it
ACCESSION NUMBER: 1998:29005751 BIOTECHNO
TITLE: The difference in recognition of terminal tripeptides as peroxisomal targeting signal I between yeast and human is due to different affinities of their receptor Pex5p to the cognate signal and to residues adjacent to it
AUTHOR: Lametschwandtner G.; Brocard C.; Fransen M.; Van Veldhoven P.; Berger J.; Hartig A.
CORPORATE SOURCE: A. Hartig, Inst. Biochem./Molek. Zellbiologie, Universitaet Wien, Vienna Biocenter, Dr Bohrgasse 9, A-1030 Wien, Austria.
E-mail: AH@abc.UniVie.AC.AT
SOURCE: Journal of Biological Chemistry, (11 DEC 1998), 273/50 (33635-33643), 55 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:29005751 BIOTECHNO
AB Pex5p is the receptor for the peroxisomal targeting signal 1 (PTS1) that consists of a C-terminal tripeptide (consensus (S/A/C)(K/R/H)(L/M)). Hexadecapeptides recognized by Pex5p from Homo sapiens and Saccharomyces cerevisiae were identified by ***screening*** a two-hybrid ***peptide*** ***library*** , and the targeting ability of the peptides was demonstrated using the green fluorescent protein as reporter. The PTS1 receptors recognized in a species- specific manner a broad range of C-terminal tripeptides, and these are reported herein. In addition, residues upstream of the tripeptide influenced the strength of the interaction in the two-hybrid system as well as in an in vitro competition ***assay*** . In peptides interacting with the human protein, ***hydrophobic*** residues were found with high frequency especially at positions - 2 and -5, whereas peptides interacting with S. cerevisiae Pex5p were more hydrophilic and frequently contained arginine at position -2. In instances where the terminal tripeptide deviated from the consensus, upstream residues exerted a greater influence on the ability of the hexadecapeptides to bind Pex5p.

L2 ANSWER 20 OF 28 BIOTECHNO COPYRIGHT 2000 Elsevier Science B.V.
TI Erythromycin resistance peptides selected from random peptide libraries

ACCESSION NUMBER: 1997:27311172 BIOTECHNO
TITLE: Erythromycin resistance peptides selected from random peptide libraries
AUTHOR: Tenson T.; Xiong L.; Kloss P.; Mankin A.S.
CORPORATE SOURCE: A.S. Mankin, Pharmaceutical Biotechnology Center, University of Illinois, 900 S. Ashland Ave., Chicago, IL 60807-7173, United States.
E-mail: shura@uic.edu
SOURCE: Journal of Biological Chemistry, (1997), 272/28 (17425-17430), 28 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27311172 BIOTECHNO
AB Translation of a 5-codon mini-gene encoded in Escherichia coli 23 S rRNA was previously shown to render cells resistant to erythromycin (Tenson, T., DeBlasio, A., and Mankin, A. S. (1996) Proc. Natl. Acad. Sci. U.S.A. 93, 5641-5646). Erythromycin resistance was mediated by a specific interaction of the 23 S rRNA-encoded pentapeptide with the ribosome. In the present study, peptides conferring erythromycin resistance were selected from in vivo expressed random ***peptide*** ***libraries*** to study structural features important for peptide activity. ***Screening*** of a 21-codon mini-gene library (the general structure ATG (NNN).sub.2.sub.0 TAA) demonstrated that only short peptides (3-6 amino acids long) conferred erythromycin resistance. Sequence comparison of erythromycin resistance peptides isolated from the 5-codon library (ATG (NNN).sub.4 TAA) revealed a strong preference for leucine or isoleucine as a third amino acid and a ***hydrophobic*** amino acid at the C terminus of the peptide. When tested against other antibiotics, erythromycin resistance peptides rendered cells resistant to other macrolides, oleandomycin and spiramycin, but not to chloramphenicol or clindamycin. Defining the consensus amino acid sequence of erythromycin resistance peptides provided insights into a possible mode of peptide action and the nature of the peptide binding site on the ribosome.

L2 ANSWER 24 OF 28 BIOTECHNO COPYRIGHT 2000 Elsevier Science B.V.
TI Substrate specificity of the DnaK chaperone determined by ***screening*** cellulose-bound ***peptide*** ***libraries***
ACCESSION NUMBER: 1997:27151945 BIOTECHNO
TITLE: Substrate specificity of the DnaK chaperone determined by ***screening*** cellulose-bound ***peptide*** ***libraries***
AUTHOR: Rudiger S.; Germeroth L.; Schneider-Mergener J.; Bukau B.
CORPORATE SOURCE: J. Schneider-Mergener, Institut Medizinische Immunologie, Universitatsklinikum Charite, Humboldt Universitat zu Berlin, Schumannstrasse 20-21, D-10098 Berlin, Germany.
SOURCE: EMBO Journal, (1997), 16/7 (1501-1507), 32 reference(s)
CODEN: EMJODG ISSN: 0261-4189
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom

LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27151945 BIOTECHNO
AB Hsp70 chaperones assist protein folding by ATP-dependent association with linear peptide segments of a large variety of folding intermediates. The molecular basis for this ability to differentiate between native and non-native conformers was investigated for the DnaK homolog of Escherichia coli. We identified binding sites and the recognition motif in substrates by screening 4360 cellulose-bound peptides scanning the sequences of 37 biologically relevant proteins. DnaK binding sites in protein sequences occurred statistically every 36 residues. In the folded proteins these sites are mostly buried and in the majority found in .beta.-sheet elements. The binding motif consists of a ***hydrophobic*** core of four to five residues enriched particularly in Leu, but also in Ile, Val, Phe and Tyr, and two flanking regions enriched in basic residues. Acidic residues are excluded from the core and disfavored in flanking regions. The energetic contribution of all 20 amino acids for DnaK binding was determined. On the basis of these data an algorithm was established that predicts DnaK binding sites in protein sequences with high accuracy.

L2 ANSWER 25 OF 28 BIOTECHNO COPYRIGHT 2000 Elsevier Science B.V.
TI Affinity purification of von willebrand factor using ligands derived from peptide libraries
ACCESSION NUMBER: 1996:26171660 BIOTECHNO
TITLE: Affinity purification of von willebrand factor using ligands derived from peptide libraries
AUTHOR: Huang P.Y.; Baumbach G.A.; Dadd C.A.; Buettner J.A.; Masecar B.L.; Hentsch M.; Hammond D.J.; Carbonell R.G.
CORPORATE SOURCE: Department of Chemical Engineering, North Carolina State University,Raleigh, NC 27695-7905, United States.
SOURCE: Bioorganic and Medicinal Chemistry, (1996), 4/5 (699-708)
CODEN: BMECEP ISSN: 0968-0896
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:26171660 BIOTECHNO
AB The chromatographic purification of vWF (von Willebrand Factor) from human plasma represents a challenge because it consists of multimers with molecular weights ranging from 0.5 to 10 million Daltons. Phage ***peptide*** ***library*** ***screening*** yielded a lead peptide (RLRSFY) that interacts with vWF. Conservative substitutions of terminal residues of the lead peptide led to a second peptide, RVRSFY, which was more efficient in the affinity chromatographic purification of vWF from protein mixtures. Adsorption isotherm measurements indicated multiple interactions between vWF and the immobilized peptide RVRSFY. Increases in peptide density on the chromatographic supports resulted in stronger association constants and higher maximum protein binding capacities. When the peptide density was lower than 32 mg/mL, there was no measurable interaction between vWF and immobilized peptide RVRSFY in HEPES buffer containing 0.5 M NaCl at pH 7. An increase in peptide density from 32 to 60 mg/mL increased the association constants from 0.9

x 10.sup.6 to 2 x 10.sup.6 (M.sup.-.sup.1). Divalent salts (calcium and magnesium chloride) were used to elute the retained vWF with 82.5% of the activity recovered. The interactions between vWF and the immobilized peptide BVRSFY are dominated by ionic attractions and also involve ***hydrophobic*** interactions at close contact. Finally, the purification of vWF from crude material PEG filtrate of a cryoprecipitate of human plasma is demonstrated using affinity chromatography with immobilized N-acetyl-RVRSFYK.

L2 ANSWER 26 OF 28 BIOTECHNO COPYRIGHT 2000 Elsevier Science B.V.
TI Selection of trypsin inhibitors in phage peptide library
ACCESSION NUMBER: 1996:26106798 BIOTECHNO
TITLE: Selection of trypsin inhibitors in phage peptide library
AUTHOR: Fang R.; Qi J.; Lu Z.-B.; Zhou H.; Li W.; Shen J.
CORPORATE SOURCE: Department of Molecular Biology, Jilin University,Changchun, 130023, China.
SOURCE: Biochemical and Biophysical Research Communications, (1996), 220/1 (53-56)
CODEN: BBRCA0 ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:26106798 BIOTECHNO
AB The newly developed techniques of ***peptide*** ***libraries*** have become a conventional and efficient method in ***screening*** ligands of proteins of interest. We present here the successful results of selection of trypsin inhibitors in a phage hexapeptide library. After affinity selection and activity ***assay*** , peptide sequences, deduced from DNA sequencing of the phage peptides with the most striking trypsin activity, share some common features with trypsin inhibitors reported. All of the phage peptides selected out and those native and synthetic trypsin inhibitors reported are composed of three parts: (a) positively charged part (Arg, Lys or their analogs); (b) polar part that may form hydrogen bonds with Ser in the active site of trypsin; (c) ***hydrophobic*** part that interacts with the nonpolar region of trypsin active site.

L11 ANSWER 20 OF 42 DRUGU COPYRIGHT 2000 DERWENT INFORMATION LTDDUPLICATE 5

AB A series of low ***molecular*** ***weight*** peptide inhibitors of factor Xa was identified by ***screening*** a combinatorial ***peptide*** ***library*** composed of L-amino acids. The peptides were subsequently modified into SEL-1915, SEL-2219, SEL-2489 and SEL-2711. The modified compounds were evaluated for inhibitory activity against factor Xa, thrombin, factor VIIa/tissue factor, plasmin, activated protein C, kallikrein and trypsin in-vitro. Furthermore, the in-vitro and in-vivo anticoagulant activities of the compounds were investigated in rabbit pooled plasma and after i.v. administration to rats and rabbits, respectively. The results showed that SEL-2489 was active in in-vitro and in-vivo coagulation ***assays*** , indicating its potential application in anticoagulant therapy.

ABEX The low ***molecular*** ***weight*** peptides initially identified were evaluated for inhibitory activity against factor XA, thrombin and trypsin. All of the peptides containing the Tyr-Ile-Arg or Phe-Ile-Arg tripeptide sequence displayed activity against factor Xa with Ki values in the range 4-15 uM. Little effect on factor Xa inhibition was seen with the removal of 3 to 4 residues from the C-terminus. However, further truncations significantly reduced the Ki values (Ki = 1.4 for D-Tyr-Ile-Arg). Factor Xa activity was completely abolished by the removal of tyrosine from the N-terminus, the replacement of isoleucine with glycine or alanine and the replacement of arginine with lysine or other amino-alkyl side chains. Ac-Tyr-Ile-Arg exhibited potent inhibitory activity against trypsin and thrombin (Ki = 0.5 and 8.2 nM, respectively), but inhibited factor Xa with a low micromolar affinity (Ki = 3.4 uM). The SAR of the initial low ***molecular*** ***weight*** peptides led to the synthesis of SEL-1915, SEL-2219, SEL-2489 and SEL-2711. All of the compounds showed factor Xa inhibitory activity with respective Ki values of 4, 0.055, 0.025 and 0.003 uM for SEL-1915, SEL-2219, SEL-2489 and SEL-2711. The most selective activity for factor Xa over thrombin, factor VIIa/tissue factor, plasmin, activated protein C, kallikrein and trypsin was displayed by SEL-2489. Furthermore, SEL-2489 inhibited prothromboplastin-induced coagulation in-vitro with an IC50 value of 0.9 uM. In the in-vivo studies, SEL-2489 dose-dependently inhibited anticoagulation in rats and rabbits. (ALT)

L11 ANSWER 22 OF 42 CEABA COPYRIGHT 2000 DECHEMA

AB Western blotting showed that TV8DCV12D, an anti-trichosanthin (TCS) monoclonal antibody, could bind to a CNBr-cleaved TCS fragment with a molecular mass of 8 kD. The epitope was located at residues 1-72 of the N-terminal of TCS as shown by amino acid analysis. A random 6-amino acid (6-aa) ***peptide*** ***library*** cloned in pIII of phage M13 was ***screened*** with TV8DCV12D. After two cycles of ***screening*** , 15 positive clones were randomly selected and 6 kinds of 6-aa sequences were determined, which were shown to be highly homologous with a Ser/Thr-(X)-X-Arg motif, where X denotes a ***hydrophobic*** amino acid. The motif is similar to the first 3-5 amino acid sequence of the TCS N-terminal. The synthesized 1-8 peptide of TCS showed competitive binding to TV8DCV12D, with native TCS. The 3-5 amino acid residues of TCS N-terminal is the core of the epitope recognized by TV8DCV12D.

L11 ANSWER 23 OF 42 DRUGNL COPYRIGHT 2000 IMSWORLD

TX Peptide Therapeutics is seeking commercial partners for development of proteinase inhibitors using RAPiD (Rational Approach to Protease Inhibitor Design), its combinatorial ***screening*** technology. The company is also seeking to collaborate with genomics companies, for exploitation of genetic data in the discovery of proteinase targets, and subsequently inhibitors of this enzyme. Peptide Therapeutics is making RAPiD available free of ***charge*** to academic establishments. The first step in the RAPiD system involves identification of substrates specific for a particular proteinase through ***screening*** of liquid phase combinatorial peptide and ***peptidomimetic*** ***libraries*** with the proteinase. The proprietary ***screening*** system enables information readily to be assimilated, and high throughput substrate ***screens*** developed. These are then ***screened*** with the proteinase, and structure activity data relating to the enzyme's active site can be generated. These data are then used for the design of peptide or peptidomimetic proteinase inhibitors. RAPiD can be used with a wide variety of proteinase inhibitor classes, and no structural information on the proteinase is required.

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SUMM There are already examples in the literature of peptide mimetics being selected from phage peptide display libraries ***screened*** against carbohydrate-binding proteins, including peptide ligands for the mannose-binding protein concanavalin A (con A) (Scott et al, Proc. Natl. Acad. Sci. USA, vol 89, pp. 5398-5402, 1992; also Oldenburg et al, Proc. Natl. Acad. Sci. USA, vol 89, pp. 5393-5397, 1992), and an anti-carbohydrate MAb (Hoess et al, Gene, vol 128, pp. 43-49, 1993). The independent results of the two groups studying con A showed strong consensus in the peptide sequences selected, including the repeated motif YPY; ***screening*** against the MAb resulted in selection of a repeated motif PWLY. There has been some speculation that the aromatic side-chains selected by both carbohydrate-binding proteins stack against each other in a similar stereochemical configuration to sugar rings. In contrast, the structure selected by MAb 55.1 lacks the ***hydrophobic*** and conformational properties of the ligands described above, was selected from a nominally cyclic ***peptide*** ***library*** , and no selection was observed on ***screening*** MAb 55.1 against linear ***peptide*** ***libraries*** generated in-house (the other groups selected binders from linear ***peptide*** ***libraries***). A search for the sequence ACEHRGSGWC in protein sequence databases has failed to show homology to any known peptides, hence the sequence bound by MAb 55.1 is novel.

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TI Substrate specificity of the DnaK chaperone determined by ***screening*** cellulose-bound ***peptide*** ***libraries***

AB Hsp70 chaperones assist protein folding by ATP-dependent association with linear peptide segments of a large variety of folding intermediates. The molecular basis for this ability to differentiate between native and non-native conformers was investigated for the DnaK homolog of Escherichia coli. We identified binding sites and the recognition motif in substrates by screening 4360 cellulose-bound peptides scanning the sequences of 37 biologically relevant proteins. DnaK binding sites in protein sequences occurred statistically every 36 residues. In the folded proteins these sites are mostly buried and in the majority found in

.beta.-sheet elements. The binding motif consists of a ***hydrophobic*** core of four to five residues enriched particularly in Leu, but also in Ile, Val, Phe and Tyr, and two flanking regions enriched in basic residues. Acidic residues are excluded from the core and disfavored in flanking regions. The energetic contribution of all 20 amino acids for DnaK binding was determined. On the basis of these data an algorithm was established that predicts DnaK binding sites in protein sequences with high accuracy.

CT *cellulose; *chaperone; *protein dnak; *enzyme specificity; *protein folding; adenosine triphosphate; heat shock protein 70; peptide; algorithm; amino acid sequence; article; binding site; escherichia coli; ***hydrophobicity*** ; priority journal; protein secondary structure; sequence homology; statistics

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AB The chromatographic purification of vWF (von Willebrand Factor) from human plasma represents a challenge because it consists of multimers with molecular weights ranging from 0.5 to 10 million Daltons. Phage ***peptide*** ***library*** ***screening*** yielded a lead peptide (RLRSFY) that interacts with vWF. Conservative substitutions of terminal residues of the lead peptide led to a second peptide, RVRSFY, which was more efficient in the affinity chromatographic purification of vWF from protein mixtures. Adsorption isotherm measurements indicated multiple interactions between vWF and the immobilized peptide RVRSFY. Increases in peptide density on the chromatographic supports resulted in stronger association constants and higher maximum protein binding capacities. When the peptide density was lower than 32 mg/mL, there was no measurable interaction between vWF and immobilized peptide RVRSFY in HEPES buffer containing 0.5 M NaCl at pH 7. An increase in peptide density from 32 to 60 mg/mL increased the association constants from 0.9 x 10.sup.6 to 2 x 10.sup.6 (M.sup.-.sup.1). Divalent salts (calcium and magnesium chloride) were used to elute the retained vWF with 82.5% of the activity recovered. The interactions between vWF and the immobilized peptide BVRSFY are dominated by ionic attractions and also involve ***hydrophobic*** interactions at close contact. Finally, the purification of vWF from crude material PEG filtrate of a cryoprecipitate of human plasma is demonstrated using affinity chromatography with immobilized N-acetyl-RVRSFYK.

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AB A bacteriophage ***peptide*** ***library*** containing a random 15-amino-acid insert was ***screened*** for identification of peptide sequence(s) that bind pp60(c-src). Sequencing the random insert from more than 100 virions indicated that more than 60% of the phage virions that bound to this enzyme contained a GXXG sequence motif in which X was frequently a ***hydrophobic*** residue. The GXXG sequence was often repeated as GXXGXXG. Two nonameric peptides were synthesized to determine whether or not the peptide inhibits pp60(c-src) tyrosine kinase activity and the importance of the glycine residues within this sequence. The peptide containing glycine had a K(i) of 24 .mu.M, whereas replacing the glycines with proline increased the K(i) value to 3.1 mM.

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AB A drug design strategy was described for non-peptide small molecule antagonists of neuropeptides, starting from substance P and CCK-36-33. The strategy targeted the molecular diversity which exists in the

privileged data set of the physico-chemical properties represented by the side-chains of the 20 genetically encoded amino-acids. The strategy was exemplified by the design of a selective and high affinity CCK-A antagonist PD-140548, CCK-B antagonist PD-134308, tachykinin NK-1 antagonist PD-154075 and NK-2 antagonist Cam-2291. The NK-3 antagonists PD-157672 and the non-peptide PD-161182, were developed from an information-rich dipeptide library constructed from 256 N-protected dipeptides and 64 ***hydrophobic*** biased dipeptides. Pharmacological data was reported for PD-154075 and PD-161182 in guinea-pig, rabbit and human tissues and in-vivo in guinea-pigs. (conference paper).

ABEX A drug design strategy was described for the production of non-peptide small molecule antagonists of neuropeptides, starting from the chemical structure of substance P and CCK-36-33 (sulfated). The strategy targeted the molecular diversity which exists in the privileged data set of the physico-chemical properties represented by the side-chains of the 20 genetically encoded amino-acids. The strategy was exemplified by the design of a selective and high affinity CCK-A antagonist PD-140548, CCK-B antagonist CI-988 (PD-134308), tachykinin NK-1 antagonist PD 154075 and NK-2 antagonist Cam-2291. The NK-3 antagonists PD-157672 and the non-peptide PD-161182, were developed from an information-rich dipeptide library constructed from 256 N-protected dipeptides and 64 ***hydrophobic*** biased dipeptides. The results of binding ***assays*** revealed the Ki of PD-154075 to be 0.35 nM vs. NK1 (IM-9). Ki values were greater than 1 uM for NK2 and NK3 receptors. KB values were 0.33, 1.8, 0.44 and 0.16 in guinea-pig ileum, guinea-pig trachea, rabbit jugular vein and guinea-pig basilar artery, respectively. ID50 of i.v. PD-154075 in a guinea-pig bladder extravasation study was 0.02 mg/kg. In binding ***assays*** using NK3 (human/CHO cells), NK3 (guinea-pig cortical membranes), NK3 (rat cerebral cortex), NK1 (IM9) and NK2 (HUB), IC50 of PD-161182 were 7, 4, 32, 3000 and 786 nM respectively. In-vitro, Ke was 0.9 and 6 Nm in human/CHO cells and guinea-pig habenulae, respectively. PD-161182 is the first example of a high affinity non-peptide antagonist for a membrane-bound receptor developed from ***screening*** a synthetic ***peptide*** ***library*** . (KP)